Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries

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Abstract

***Objective*—To examine whether the reduction in mortality after standard titre measles immunisation in developing countries can be explained simply by the prevention of acute measles and its long term consequences.**

***Design*—An analysis of all studies comparing mortality of unimmunised children and children immunised with standard titre measles vaccine in developing countries.**

***Studies*—10 cohort and two case-control studies from Bangladesh, Benin, Burundi, Guinea-Bissau, Haiti, Senegal, and Zaire.**

***Main outcome measures*—Protective efficacy of standard titre measles immunisation against all cause mortality. Extent to which difference in mortality between immunised and unimmunised children could be explained by prevention of measles disease.**

***Results*—Protective efficacy against death after measles immunisation ranged from 30% to 86%. Efficacy was highest in the studies with short follow up and when children were immunised in infancy (range 44-100%). Vaccine efficacy against death was much greater than the proportion of deaths attributed to acute measles disease. In four studies from Guinea-Bissau, Senegal, and Burundi vaccine efficacy against death remained almost unchanged when cases of measles were excluded from the analysis. Diphtheria-tetanus-pertussis and polio vaccinations were not associated with reduction in mortality.**

***Conclusion*—These observations suggest that standard titre measles vaccine may confer a beneficial effect which is unrelated to the specific protection against measles disease.**

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Introduction

Evaluations of immunisation programmes are usually based on the assumption that vaccines have an impact only against specific diseases. This assumption may not be correct for measles vaccine. Recent studies indicate that vaccines may have important non-specific effects as girls receiving high titre measles vaccines were found to have reduced long term survival compared with recipients of standard titre vaccines.[1-3] On the other hand, studies of standard titre measles vaccine have reported a greater than expected reduction in mortality in areas with high mortality.[4-6] As these observations suggest that measles immunisation may have a non-specific, beneficial effect[5] we reviewed mortality studies of unvaccinated and vaccinated children and examined whether the reduction in mortality after measles immunisation is due only to the specific prevention of acute measles disease and its long term consequences. If measles vaccines have non-specific, beneficial effects the age at immunisation and the number of doses of vaccines should be reconsidered. Furthermore, new measles vaccines would have to be evaluated for their impact on survival before being introduced, and immunisation would have to continue after possible eradication of measles unless the same beneficial effects could be produced through other means.

Studies and methods

STUDIES OF STANDARD TITRE MEASLES VACCINE

We reviewed *Index Medicus* from 1970 onwards for studies dealing with mortality after standard titre measles vaccination. Table I shows the available studies with information on mortality among immunised and unimmunised children. We found 10 follow up studies and two case-control studies which had examined the impact of Schwarz standard titre measles vaccine.

STUDIES OF DIPHTHERIA-TETANUS-PERTUSSIS AND POLIO IMMUNISATION

Reduced mortality among recipients of standard titre measles vaccine compared with unimmunised children could be due to a selection bias between those children who attended and those who did not attend clinics for measles vaccination. We therefore examined whether diphtheria-tetanus-pertussis and polio vaccination was associated with a similar reduction in the areas where measles vaccine had also been examined. Attendance for diphtheria-tetanus-pertussis and polio vaccinations is probably associated with attendance for later measles immunisation. Therefore, any separate impact of these vaccines has to be examined at ages before measles immunisation. The only published study of this effect was a case-control study from Benin.[16] Relevant data, however, were available from both Senegal and Guinea-Bissau.

We examined the impact of diphtheria-tetanus-pertussis and polio vaccines on mortality in children between 5 and 10 months of age in Niakhar, Senegal.[2,12] At 5 months children were called for immunisation and some attended and received diphtheria-tetanus-pertussis, inactivated polio vaccine, and placebo for measles vaccine whereas others did not attend. At 10 months of age the children were called again for measles immunisation. The estimate of mortality ratio between 5 and 10 months was adjusted for previous immunisations at 3 months of age.

In Guinea-Bissau we used data from a national cluster sample of 10 000 women of fertile age and their prospectively registered pregnancies (authors' unpublished data). Women of fertile age and their children were visited about every six months. In the present analysis we included only children whose immunisation card was seen and children who were assumed to be unvaccinated because they had no card. Children aged 2-3 months when first seen should have been immunised with diphtheria-tetanus-pertussis and oral polio vaccines and within six months of follow up they would not have received measles vaccine. Some children may have received other diphtheria-tetanus-pertussis and oral polio vaccines during follow up, but it was not possible to get full immunisation information for children who had died, moved, or were absent at the re-examination. To examine whether any vaccine is a marker for better survival we compared mortality of children aged 2-3 months during six months of follow up according to their immunisation status when first seen.

DEFINITIONS AND STATISTICAL METHODS

We have emphasised the crude estimates of mortality differences based on deaths by person years at

TABLE I—*Studies of measles vaccine*

Country	Year	Type of study	Sample size	Measles surveillance*	Death ascertainment	Confounder control
Zaire[7]†	1974-7	Different areas	2160 Person years at risk	Three monthly survey	Three monthly survey	None
Guinea-Bissau I[8]	1981-2	Same area	211 Children	Six monthly survey	Six monthly survey	None
Guinea-Bissau II[9]‡	1980	Same area	432 Children	Survey	Three monthly survey	None
Guinea-Bissau III[9]§	1984-6	Different groups	177 Children	Active	Three monthly survey	Twins, orphan
Guinea-Bissau IV[10]	1984-7	Same area	722 Children	Active	Three monthly survey	Sex, age, district
Senegal I[11]‖	1965-8	Different areas	7097 Person years at risk	No information	Yearly	None
Senegal II[12]	1987-91	Same area	4222 Children	Active	Weekly	None
Burundi[13]¶	1988-9	Same area	1899 Children	Survey	Six Months later	None
Haiti[14]**	1982-5	Same area	1362 Children	None	30 Months later	Cement walls, literacy, knowledge of oral rehydration solution, spacing
Bangladesh I[6]	1982-4	Different areas, case-control	536 Deaths, 1072 controls	Thrice weekly	Thrice weekly	Sex, family size, education, ownership of land, religion
Bangladesh II[15]††	1982-5	Different areas	16 270 Children	Thrice weekly	Thrice weekly	Sex, parity, size of dwelling, education
Benin[16]‡‡	1986-7	Same area, case-control	74 Deaths, 230 controls	18 Months later	18 Months later	Socioeconomic status, weight for age, other vaccines

*Interval between collection of information on measles disease. Active=case identified during active phase of disease.
†Compared immunised children in one area with unimmunised children in a different area.
‡Mortality compared for children attending outreach clinic who were vaccinated against measles with children who did not attend because of temporary absence. In year before introduction of vaccine mortality was the same in those who did and did not attend clinic.
§Study represents "natural experiment." During one year blood samples were collected before and after vaccination. When samples were analysed with delay of two years, it turned out that during short period of three weeks, children had not seroconverted. These children can be considered to have received "placebo." Mortality is compared for "placebo" recipients and seroconverters in same study. Study has been considered to compare two different groups rather than immunised and unimmunised within same community.
‖Two measles vaccination campaigns were carried out in certain villages in one rural area of Senegal. Immunised children were compared with children from unimmunised villages. Only children immunised before 3 years of age have been included in the present analysis to make age range comparable with age of immunisation used in most other studies.
¶Age adjusted information according to vaccination and measles disease status was not included in paper but was provided by authors (RT Chen, personal communication).
**Study provided estimates for children according to antibody status at time of immunisation and according to seroconversion. In present analysis, we compared all immunised children, irrespective of initial antibody titre, with unvaccinated children as this is available information from other studies. Specific person years at risk were not reported, but it has been assumed that all survivors were followed on average for 30 months and children who died for 6 months.
††Before introduction of measles immunisation mortality was similar in two areas being compared. After 1985, when children in control district had also received measles immunisation, mortality in two areas was again similar (authors' unpublished observations).
‡‡Published paper reports only efficacy by age at vaccination (≤12 months and ≥12 months). Combined estimate for all ages is presented here (J P Velema, personal communication).

risk available for all the follow up studies, but available multivariate estimates adjusted for significant background factors have also been noted in table II. Vaccine efficacy against death (VED) was calculated as one minus the mortality rate ratio between immunised and unimmunised children. We tested the homogeneity of the estimates of vaccine efficacy against death—that is, the hypothesis of no interaction between study and the size of the vaccine effect.[17] The Mantel-Haenszel estimator was used to combine results from different subgroups.

Death from acute measles is usually defined as any death within one month[8] or six weeks[18] of a measles rash. In the present analyses we used the definition used by the study in question. Mortality after measles was considered as any death after the acute phase of measles, irrespective of whether it could be directly linked to measles disease. The possible impact of immunisation beyond the prevention of measles disease was assessed by comparing the mortality of immunised, uninfected children and unimmunised, uninfected children. This was possible in four studies (Guinea-Bissau III and IV, Senegal II and Burundi) by censoring follow up at the time of measles disease, thus excluding both death after acute measles and deaths after measles.

Results

REDUCTION IN CHILDHOOD MORTALITY AFTER STANDARD TITRE MEASLES VACCINE

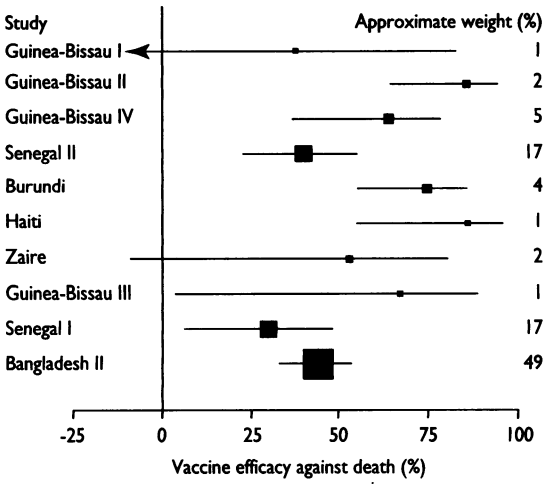
Table II shows that in all 10 follow up studies the impact on mortality after standard measles immunisation was large, showing reductions in the range of 30-86%. The two case-control studies suggested similar reductions in mortality. Crude and adjusted estimates were virtually identical. All follow up studies showed large reductions, but the estimates of vaccine efficacy against death were heterogeneous (test for homogeneity, $\chi^2=26{\cdot}3$; df=9; P=0·002; figure).

The follow up studies were of two kinds. The first kind compared attenders and non-attenders within the same community; vaccine efficacy against death was in the range of 38-86%. In studies comparing immunised and unimmunised children from different communities estimates of vaccine efficacy against death were less heterogeneous, showing estimates in the range of 30-67%. Other forms of heterogeneity, however, may have been more important for the variation in estimates in table II. The impact tended to be greatest in the studies when children were immunised early[5] and which had a short follow up. For example, in seven studies from Zaire, Guinea-Bissau (I-IV), and Senegal (I-II) with further data available vaccine efficacy

TABLE II—*Mortality (deaths/person years at risk) and vaccine efficacy against death of standard titre measles vaccine*

Country	Age at vaccination (months)	Median follow up (months)	Mortality		Vaccine efficacy (%) (95% confidence interval)		Measles deaths among unvaccinated children
			Unvaccinated	Vaccinated	Crude	Adjusted*	
Follow up studies:							
Immunised and unimmunised from same community							
Guinea-Bissau I	6-36	13	5/75·3	7/170·3	38 (−95 to 80)		0% (0/5)
Guinea-Bissau II	6-35	12	10/70·5	7/361·0	86 (64 to 95)		0% 0/10)
Guinea-Bissau IV	9-23	19	34/367·5	20/595·8	64 (37 to 79)	66 (32 to 83)	18% (6/34)
Senegal II	9-18	23	86/1610·5	90/2806·7	40 (19 to 55)		3% (3/86)
Burundi	9-23	15	51/1083·4	14/1201·2	75 (55 to 86)		22% (11/51)
Haiti	6-13	30	70/2500·0	3/759·0	86 (55 to 96)	90 (59 to 98)	0% (0/70)
Immunised and unimmunised children from different communities/groups							
Zaire	7-9	24	66/1811·2	6/348·8	53 (−9 to 80)		NA
Guinea-Bissau III	7-24	24	7/92·8	6/244·6	67 (3 to 89)	83 (35 to 95)	29% (2/7)
Senegal I	6-35	32	1104/6699	46/397·6	30 (6 to 48)		14% (155/1104)
Bangladesh II	9-60	22	339/14 940	195/15 327	44 (33 to 53)	46 (35 to 95)	NA
Case-control studies							
Bangladesh I	9-60		536 deaths		36 (21 to 48)	36 (20 to 50)	4% (21/536)†
Benin	9-23		74 deaths		45 (−7 to 72)	‡	9% (7/74)†

*Adjusted for significant background factors for mortality (see table 1).
†In case-control studies proportion of deaths due to measles is related to total group of deaths and not to group of unimmunised children.
‡Estimates were said to be the same in multivariate analysis.
NA=not available.



Measles vaccine efficacy against death in 10 studies from developing countries. Solid squares represent vaccine efficacy against death (one minus the rate ratio of mortality) in individual studies and lines denote 95% confidence intervals. Size of squares is proportional to reciprocal variance of estimate, amount of "information" contributed to that study, also given by approximate weights in percentage of total amount of information in all 10 studies.

against death was higher, being in the range of 44-100%, when the analysis was limited to one year of follow up for children immunised in infancy than in the residual part of these studies (data available on request). In the Bangladesh II study, in which the mortality data were presented in three monthly intervals,[15] vaccine efficacy against death was significantly greater in the first 24 months after immunisation (48%; 95% confidence interval 37% to 57%) than in the last 21 months of the study (6%; −46% to 40%) (χ^2=5·75; df=1; P=0·016). There were similar tendencies in the studies from Zaire, Senegal II, and Guinea-Bissau IV (data available on request).

STANDARD TITRE MEASLES VACCINE: PREVENTION OF ACUTE AND LONG TERM CONSEQUENCES OF MEASLES

As indicated in table II all studies found the reduction in mortality after measles immunisation to be much larger than the proportion of deaths attributed to acute measles disease. It has therefore been speculated that the prevention of delayed deaths from measles could explain the reduction.[6] This could be tested by comparing mortality of unimmunised and immunised children after the exclusion of all cases of measles. If the impact of vaccine was related only to the specific prevention of the acute and long term consequences of measles disease there should be no difference in mortality according to immunisation status among uninfected children. This, however, was not the case in any of the studies (table III). In the three larger studies—Guinea-Bissau IV, Senegal II, and Burundi—there was no change in vaccine efficacy against death after exclusion of all cases of measles. Hence, in these studies the prevention of measles contributed little to the reduction in mortality associated with immunisation.

DIPHTHERIA-TETANUS-PERTUSSIS AND POLIO IMMUNISATIONS: NO ASSOCIATION WITH REDUCED CHILDHOOD MORTALITY

We also examined the impact of diphtheria-tetanus-pertussis and polio vaccines in areas where measles immunisation had been studied. In the case-control study from Benin recipients of one dose of diphtheria-tetanus-pertussis and oral polio tended to have higher mortality than unimmunised children (relative risk=2·20; 95% confidence interval 0·93 to 5·22).[16] In the vaccine trial from Senegal II (table IV) the 638 children attending at 5 months and receiving diphtheria-tetanus-pertussis and inactivated polio vaccine (and placebo for measles vaccine) had slightly but not significantly higher mortality between 5 and 10 months of age than the 607 children not attending immunisation at 5 months (Mantel-Haenszel, mortality ratio=1·60; 0·76 to 3·37). In the cluster cohort study of 10 000 women of fertile age and their children in Guinea-Bissau 488 children were 2-3 months old when first seen. During six months of follow up mortality was 4% (9/245) for children who had already received diphtheria-tetanus-pertussis and oral polio vaccines at least once and 3% (8/243) for children who had not received these vaccines.

Discussion

In our analysis of studies on the protective efficacy against death of standard measles immunisation we found a reduction in mortality in the range of 30-86%. A major reduction in mortality after measles immunisation is also supported by a few studies comparing mortality rates before and after the introduction of measles vaccination.[19,20] Though estimates were heterogeneous the reduction in mortality was considerably larger in all studies than the share of deaths attributed to acute measles disease in the same areas (table II). Surprisingly, the protective efficacy of measles vaccine was virtually unchanged when follow up was discontinued at the date of measles disease, suggesting that the reduction in mortality after measles immunisation may have little to do with the specific prevention of measles. Subclinical measles infection is rare after the age of measles immunisation,[21] and it seems therefore unlikely that undetected measles infection is a major cause of higher mortality in the unimmunised group, particularly because clinical measles explained little of the difference in mortality. Several other observations also support the possibility that measles vaccine has non-specific effects. Contrary to expectations, several studies indicated that measles immunisation is particularly effective when given early in life.[4,5,7,9,16] Furthermore, the reduction in mortality may be the greatest during the first year after immunisation as a higher vaccine efficacy was observed when the follow up period was limited to one year.[7,10,12,15] Though few studies have reported data by sex it seems that standard vaccine may be more beneficial for girls than for boys.[12,19,22]

Double blind placebo trials of standard titre measles vaccine on mortality in developing countries have not been performed, and as differences in mortality were not explained by prevention of measles the difference between immunised and unimmunised children could reflect an association between measles immunisation and access to other health interventions or a selection bias. Most studies (Bangladesh I and II, Guinea-Bissau I, II, and III, Senegal I, Zaire) excluded an association with other health interventions because measles

TABLE III—*Measles vaccine efficacy against death, including and excluding cases of measles*

Study	Efficacy (%) (95% confidence interval) (including measles cases)	Deaths after measles	Measles cases	Efficacy (%) (95% confidence interval (excluding measles cases)
Guinea-Bissau III	67 (3 to 89)	4	20	35 (−162 to 84)
Guinea-Bissau IV	64 (37 to 79)	13	125	65 (35 to 81)
Senegal II	40 (19 to 55)	8	92	40 (18 to 55)
Burundi	75 (55 to 86)	22	357	74 (48 to 87)

TABLE IV—*Mortality between 5 and 10 months of age according to status for diphtheria-tetanus-pertussis and inactivated polio vaccine (DTP-IPV) vaccination, Niakhar, Senegal, 1987-9*

Previous DTP-IPV immunisation at 3 months	Deaths/population (%) for DTP-IPV vaccine at 5 months	
	Immunised	Unimmunised
Yes	6/113 (5%)	10/338 (3%)
No	11/525 (2%)	4/269 (1%)
Total	17/638 (3%)	14/607 (2%)

Key messages

- Studies from developing countries have reported reductions in childhood mortality after the introduction of standard titre immunisation for measles
- In 10 cohort studies measles efficacy against death was in the range of 30-86%
- The specific prevention of the acute and long term consequences of measles disease does not explain the reduction in mortality among immunised children
- In three studies diphtheria-tetanus-pertussis and polio vaccines were not associated with similar reductions in mortality, making it unlikely that selection bias can explain the impact of measles immunisation
- Standard titre measles vaccine seems to be associated with a non-specific, beneficial effect which may have important implications for the planning of immunisation programmes

immunisation was the only intervention available or the only intervention which differed between the areas. Most studies (Bangladesh I and II, Guinea-Bissau II, III, and IV, Haiti, Zaire) tried to exclude the possibility that selection bias was the major cause of differences in mortality by using multivariate analysis to adjust for important determinants of mortality (table II), by showing no difference between the groups before the introduction of measles vaccine, or by comparing those who did not seroconvert because they had received a placebo and children who had received an effective vaccine.

A bias due to publication of only those studies with significant results seems unlikely as a strong effect of measles immunisation has been reported from almost all the longitudinal research on measles or measles immunisation.[4 6-12 14 15 18 19 23] Though the estimate for vaccine efficacy against death was slightly lower (30-67%) for the more satisfactory studies comparing immunised and unimmunised areas than for the other studies (38-86%) comparing immunised and unimmunised children from the same area, all studies documented the same unexplained reduction in mortality.

If a systematic selection bias between attenders and non-attenders was the main cause of the clear impact of measles immunisation a similar difference in mortality could be expected between recipients and non-recipients of diphtheria-tetanus-pertussis and polio vaccines, particularly as these vaccines are given early in life when mortality is high. In the three areas with relevant data, there was no indication that immunisation with these vaccines were also associated with reduced mortality.

The observation that exclusion of cases of measles had little effect on the vaccine efficacy against death contradicts previous studies that suggest that measles is associated with a significant long term excess mortality.[4 24] Previous studies compared mortality after measles with mortality in immunised controls, however, rather than with unimmunised children who are the appropriate controls if measles immunisation has non-specific effects. For example, children who had survived the acute phase of measles in Guinea-Bissau were found to have significantly higher mortality than community controls who had received measles vaccine (mortality ratio 4·18; 1·13 to 15·43).[4] Compared with unimmunised controls, however, children who survived the acute phase did have slightly lower mortality (0·45; 0·14 to 1·43). More recent analyses of the long term effect of measles disease in Guinea-Bissau, Senegal, Bangladesh (authors' unpublished observation), and Burundi[13] indicate that children who survive acute measles have the same or significantly lower mortality than non-infected unimmunised children. Hence, acute mortality may partly be compensated by lower subsequent mortality, and the total mortality impact of measles in the unimmunised group may be limited.

If protection against measles disease does not explain the impact of measles immunisation on child survival the simplest explanation would seem to be that measles vaccine activates the immune system in a non-specific way providing protection against other infections. Studies of immune responses to measles infection have mainly focused on immunological abnormalities possibly explaining the expected immunosuppression and increased susceptibility to other infections leading to complications and death.[25] Immunological stimulation by measles disease and immunisation, however, may also protect against other infections.[26 27] For example, measles immunisation reduces the incidence of diarrhoea (authors' unpublished observation) and may prevent subsequent immunisation with vaccinia.[26]

The hypothesis of a non-specific beneficial effect of measles vaccine has important practical and theoretical implications. If new vaccines do not provide similar non-specific effects, new measles vaccines capable of immunising in the presence of maternal antibodies[28] may end up being associated with lower survival than standard titre measles vaccine. The available data indicate that child survival might benefit from standard titre measles immunisation before 9 months of age and possibly also from repeated doses of the vaccine.[5] Further studies are obviously needed to explain the biological basis and to determine the magnitude of the non-specific effects. Such studies may be conducted within two dose trials or studies of the impact of reimmunisations. Should the hypothesis be correct measles immunisation may have to be continued even when measles infection has been eradicated.

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Statistics Notes

Absence of evidence is not evidence of absence

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The non-equivalence of statistical significance and clinical importance has long been recognised, but this error of interpretation remains common. Although a significant result in a large study may sometimes not be clinically important, a far greater problem arises from misinterpretation of non-significant findings. By convention a P value greater than 5% (P>0·05) is called "not significant." Randomised controlled clinical trials that do not show a significant difference between the treatments being compared are often called "negative." This term wrongly implies that the study has shown that there is no difference, whereas usually all that has been shown is an absence of evidence of a difference. These are quite different statements.

The sample size of controlled trials is generally inadequate, with a consequent lack of power to detect real, and clinically worthwhile, differences in treatment. Freiman *et al*[1] found that only 30% of a sample of 71 trials published in the *New England Journal of Medicine* in 1978-9 with P>0·1 were large enough to have a 90% chance of detecting even a 50% difference in the effectiveness of the treatments being compared, and they found no improvement in a similar sample of trials published in 1988. To interpret all these "negative" trials as providing evidence of the ineffectiveness of new treatments is clearly wrong and foolhardy. The term "negative" should not be used in this context.[2]

A recent example is given by a trial comparing octreotide and sclerotherapy in patients with variceal bleeding.[3] The study was carried out on a sample of only 100 despite a reported calculation that suggested that 1800 patients were needed. This trial had only a 5% chance of getting a statistically significant result if the stated clinically worthwhile treatment difference truly existed. One consequence of such low statistical power was a wide confidence interval for the treatment difference. The authors concluded that the two treatments were equally effective despite a 95% confidence interval that included differences between the cure rates of the two treatments of up to 20 percentage points.

Similar evidence of the dangers of misinterpretation of non-significant results is found in numerous meta-analyses (overviews) of published trials, when few or none of the individual trials were statistically large enough. A dramatic example is provided by the overview of clinical trials evaluating fibrinolytic treatment (mostly streptokinase) for preventing reinfarction after acute myocardial infarction. The overview of randomised controlled trials found a modest but clinically worthwhile (and highly significant) reduction in mortality of 22%,[4] but only five of the 24 trials had shown a statistically significant effect with P<0·05. The lack of statistical significance of most of the individual trials led to a long delay before the true value of streptokinase was appreciated.

While it is usually reasonable not to accept a new treatment unless there is positive evidence in its favour, when issues of public health are concerned we must question whether the absence of evidence is a valid enough justification for inaction. A recent publicised example is the suggested link between some sudden infant deaths and antimony in cot mattresses. Statements about the absence of evidence are common —for example, in relation to the possible link between violent behaviour and exposure to violence on television and video, the possible harmful effects of pesticide residues in drinking water, the possible link between electromagnetic fields and leukaemia, and the possible transmission of bovine spongiform encephalopathy from cows. Can we be comfortable that the absence of clear evidence in such cases means that there is no risk or only a negligible one?

When we are told that "there is no evidence that A causes B" we should first ask whether absence of evidence means simply that there is no information at all. If there are data we should look for quantification of the association rather than just a P value. Where risks are small P values may well mislead: confidence intervals are likely to be wide, indicating considerable uncertainty. While we can never prove the absence of a relation, when necessary we should seek evidence against the link between A and B—for example, from case-control studies. The importance of carrying out such studies will relate to the seriousness of the postulated effect and how widespread is the exposure in the population.

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